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Differing neuropsychological and neuroanatomical correlates of abnormal reading in early-stage semantic dementia and dementia of the Alzheimer type

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Abstract

Individuals with semantic dementia (SD) were differentiated neuropsychologically from individuals with dementia of the Alzheimer type (DAT) at very mild-to-mild stages (clinical dementia rating 0.5 or 1). A picture naming and recognition memory experiment provided a particularly useful probe for early identification, with SD individuals showing preserved picture recognition memory and impaired naming, and DAT individuals tending to show the reverse dissociation. The identification of an early SD group provided the opportunity to inform models of reading by exploring the influence of isolated lexical semantic impairment on reading regular words. Results demonstrated prolonged latency in both SD and DAT group reading compared to a control group but exaggerated influence of frequency and length only for the SD group. The SD reading pattern was associated with focal atrophy of the left temporal pole. These cognitive-neuroanatomical findings suggest a role for the left temporal pole in lexical/semantic components of reading and demonstrate that cortical thickness differences in the left temporal pole correlate with prolonged latency associated with increased reliance on sublexical components of reading.

Keywords: Semantic dementia; Alzheimer's; Frontotemporal dementia; Reading; Recognition memory

1. Introduction

Semantic dementia (the temporal variant of frontotemporal dementia; FTD) and dementia of the Alzheimer type (DAT) are clinically overlapping diseases sharing features such as insidious onset and gradual deterioration of comprehension and word finding ability, among other impairments. Despite clinical similarities, SD is pathologically distinct from DAT (Hodges, Garrard, & Patterson, 1998; Neary et al., 1998; see also Kertesz, Hudson, Mackenzie, & Munoz, 1994). Because treatments are increasingly likely to target specific neurodegenerative mechanisms, it is important to determine whether neuropsychological markers can differentiate SD from DAT early in the course of dementia, when intervention may be most effective.

Semantic dementia (SD) is the variant of FTD involving initially focal degeneration of one or both temporal lobes

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(Hodges, Patterson, Oxbury, & Funnell, 1992; Neary et al., 1998; Snowden, Goulding, & Neary, 1989; see also Warrington, 1975). SD is similar to the fluent variety of primary progressive aphasia (Mesulam, 1982) with additional impairment of non-verbal semantic knowledge (Hodges et al., 1992; Mesulam, 2001). Distinguishing early forms of SD from DAT neuropsychologically presents a challenge because DAT can also involve deficits on semantic processing tasks (Huff, Corkin, & Growden, 1986; Kertesz, Appell, & Fisman, 1986; Martin & Fedio, 1983) even relatively early in the disease (Chertkow & Bub, 1990; Hodges & Patterson, 1995). Similarly, although episodic memory impairment is a hallmark of early DAT, simple tests of verbal episodic memory such as logical paragraph recall cannot distinguish between the two dementias because both types of patients perform poorly, SD patients due primarily to impaired language and DAT patients due primarily to impaired memory (Hodges et al., 1999). Importantly, though, semantic impairment is variable in early DAT (Hodges & Patterson, 1995) and visuospatial and attentional-executive functioning are preserved in early SD (Hodges et al., 1992; Neary et al., 1998), suggesting that SD and DAT can be distinguished early in the dementia process. For example, Hodges et al. (1999) found that a relatively early SD group (mean mini-mental state exam (MMSE) = 20) was distinguished from an early DAT group (mean MMSE = 23) by significantly better performance on a test of picture reproduction.

A related cognitive domain, which may be preserved in SD compared to DAT is picture recognition memory. Recent evidence suggests that recognition memory for pictures is preserved in the majority of SD patients (Graham, Becker, & Hodges, 1997; Graham, Simons, Pratt, Patterson, & Hodges, 2000a; Simons, Graham, & Hodges, 2002a; Simons et al., 2002b). This stands in contrast to the marked picture naming deficits in SD relative to DAT. An outstanding issue in this area involves the timing of the emergence of the picture naming/recognition memory double dissociation between SD and DAT. If naming is impaired and picture recognition memory is preserved in early SD, and the reverse dissociation is evident in early DAT, then tests of picture naming/recognition memory might provide an important and relatively simple neuropsychological tool aiding differential diagnosis. A picture naming/recognition memory experiment was conducted to explore this issue.

The identification of an early SD group provided the opportunity to inform models of reading by exploring the influence of isolated lexical semantic impairment on reading words with regular spelling-to-sound correspondences. Individuals with SD show marked impairment in reading irregular words (e.g., *glove*) (Graham, Hodges, & Patterson, 1994; Graham, Patterson, & Hodges, 2000b; Patterson & Hodges, 1992), but the available data indicate little or no impairment in reading regular words (Graham et al., 1994, 2000b; Patterson & Hodges, 1992). Little research in this area has examined latencies of SD reading (naming). Latency may provide a sensitive index of subtle reading abnormalities that may exist in reading regular words in early SD and DAT. In particular, the apparently graded degrees of lexical semantic memory retention between healthy older individuals (retained), individuals with DAT (less retained), and individuals with SD (least retained), raises interesting questions about potential for differing influences of lexical and sublexical variables in reading between groups. Such effects have the potential to inform models of reading.

Finally, to identify neuroanatomical correlates of potentially differing reading patterns between groups, structural MRI was conducted and automated brain volume analyses and a sensitive cortical thickness technique were used to compare group differences in brain volume and local mean cortical thickness in vivo (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000; Fischl, Liu, & Dale, 2001; Fischl, Sereno, & Dale, 1999a; Fischl, Sereno, Tootell, & Dale, 1999b).

2. Methods

2.1. Subjects

Three groups consisting of a total of 30 individuals participated in the study: six with early SD (four males and two females), 10 with early DAT (seven males and three females) and 14 non-demented (eight males and six females). Subjects were recruited from the Washington University's Alzheimer's Disease Research Center (ADRC) and screened for depression, severe hypertension and other medical factors described previously (Berg et al., 1998). Potential SD subjects were identified either clinically or psychometrically. Clinically, potential SD subjects were identified as having prominent word finding difficulty, relative preservation of orientation to time and place, and relative maintenance of activities of daily living (Hodges et al., 1992). Psychometrically, potential SD subjects were identified as having probable semantic impairment via general ADRC test scores (Cortese, Balota, Sergent-Marshall, & Buckner, 2003).

A specially designed neuropsychological battery was administered to identify those individuals meeting original (Hodges et al., 1992) and consensus (Neary et al., 1998) inclusion and exclusion criteria for SD; namely, impairment in semantic memory causing anomia and deficits of spoken and written single word comprehension, a reading pattern of surface dyslexia, and impoverished knowledge about objects and/or people with relative sparing of phonological and syntactic components of speech output, and perceptual and non-verbal problem solving skills. Early DAT subjects were matched approximately with the SD group for global dementia severity and years of education. SD has an earlier age of onset than DAT (Neary et al., 1998). Therefore, in order to recruit representative samples of each group, patient groups were not matched for age. Diagnosis of probable DAT was made according to criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders

Association (McKhann et al., 1984). Convergent estimates of global dementia severity were sought through scores on the clinical dementia rating (CDR; Morris, 1993), the MMSE (Folstein, Folstein, & McHugh, 1975) and whole-brain volume based on MRI. Control subjects were matched approximately with the patient groups for years of education and matched with the DAT group for age. Written informed consent was obtained from all subjects in the study, which was approved by the Human Studies Committee of Washington University.

3. Identifying semantic dementia

3.1. Multimodal semantic assessment

A battery of tests was used to assess semantic knowledge across input and output modalities and verbal and pictorial domains (similar to Chertkow & Bub, 1990; Hodges et al., 1992). A core component of the battery was a set of 64 line drawings from the Snodgrass and Vanderwart (1980) corpus, normed for frequency and prototypicality across six semantic categories: animals, birds, fruit, household items, tools, and vehicles (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000). The following tests were conducted using the set of 64 normed items:

1. Category fluency: producing as many exemplars as possible in 1 min/category.
2. Naming of all 64 line-drawings without cueing.
3. Word-to-picture matching: pointing to the drawing corresponding to a spoken word from picture arrays containing nine within-category foils.
4. Picture sorting: sorting of individual cards into various superordinate categories. First, all cards were sorted into piles of natural and human-made things. Cards representing natural things were then sorted into piles of animals/birds/fruit. Finally, cards representing human-made things were sorted into piles of tools/household items/vehicles. Sheets with written labels reflecting the desired sort (i.e., natural and human-made, etc.) were positioned in front of subjects during each sort.

Additional tests of semantics included animal fluency [from the Boston Diagnostic Aphasia Examination (BDAE); Goodglass & Kaplan, 1983], the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), the American Version of Nelson Adult Reading Test (Grober & Sliwinski, 1991), and a Synonym Test (Lambon Ralph et al., unpublished). As an additional test of non-verbal semantic knowledge, the picture version of the Pyramids and Palmtrees test (Howard & Patterson, 1992) was administered.

3.2. Fluency and comprehension assessment

The cookie theft picture and the comprehension section from the BDAE were administered to assess verbal fluency and auditory comprehension, respectively. Verbal output was rated for melodic line, phrase length, articulatory agility and grammatical form.

3.3. Visuospatial and attentional-executive function assessment

Measures used to assess visuospatial skills were Raven's Colored Progressive Matrices (Raven, 1995), block design from the WAIS (Wechsler, 1955) and various subtests from the Visual Object and Space Perception battery (Warrington & James, 1991). Measures used to assess attentional-executive function were the digit symbol subtest from the WAIS, the digit span subtests from the Wechsler Memory Scale (Wechsler & Stone, 1973), and the trails tests (Armitage, 1945).

3.4. Analyses

The goal of analyses was to identify individuals meeting consensus criteria for SD. Scores on all tests were first converted to *z*-scores for all subjects relative to the mean of the controls. Individual *z*-scores were then averaged across a number of cognitive domains to obtain reliable composite scores for lexical semantic, pictorial semantic, visuospatial, attentional-executive, speech and comprehension domains. SD is known to involve relative preservation of visuospatial and attentional-executive function as well as fluent speech (Hodges et al., 1992; Snowden et al., 1989). Individuals with SD were therefore identified as demonstrating a pattern of scores reflecting: lexical semantics impaired relative to visuospatial functioning; lexical semantics impaired relative to attentional-executive functioning; pictorial semantics impaired relative to visuospatial functioning; comprehension impaired relative to speech fluency. Results are presented for those individuals meeting consensus criteria for SD and for all DAT and control subjects.

3.5. Experiment 1: picture naming and picture recognition memory

Five of the six SD individuals and all other subjects (10 DAT and 14 control) completed the naming/recognition memory experiment. Subjects were asked to name each of the 64 Snodgrass and Vanderwart (1980) line drawings used in the semantic battery without cueing. Thirty minutes following the naming task (during which time non-pictorial tasks were given) a surprise recognition test was administered in which subjects were asked to point to the drawing they saw earlier during the naming task from among two category matched foils. The three drawings were presented side-by-side on a single card. Targets were 32 drawings selected randomly from the items used in the naming test. Foils were 64 drawings from the Snodgrass and Vanderwart (1980) corpus that were not part of the semantic test battery and were matched with targets for superordinate semantic category and

frequency. Positioning of target items among foils was counterbalanced across three spatial positions on pictorial arrays. Orientation of all drawings was identical to target orientation at naming. Drawings were scaled to half the size of those used for the naming task.

3.6. Experiment 2: word naming

Nine of the 10 DAT individuals and all other subjects (six SD and 14 control) completed the word naming experiment. The word naming experiment was part of an experiment examining potential semantic priming differences between groups. The word naming component of the priming experiment required subjects to read the second word in prime–target pairs. This manipulation allowed for computation of naming accuracy and latency to be examined across targets and as a function of specific target properties (e.g., length and frequency). Latencies were also computed based upon prime–target relationships. However, the priming manipulation yielded largely null findings, so results will only be presented for target word naming, which yielded robust between-group results. The experiment was controlled by a PC with a 133 MHz processor running in DOS mode. The 17 in. monitor was set to 40-column mode for the presentation of stimuli. A voice key (Gerbrands G1341T) was connected to the PC's real-time clock to collect response latencies to the nearest ms. Targets were 162 monosyllable words of moderately high-frequency (mean = 140.6 per million words, Kucera & Francis, 1967) with a mean length of 4.13 letters. An additional 138 multisyllabic prime–target pairs were included but not considered further due to difficulty rating them for regularity. All targets contained regular grapheme-to-phoneme correspondences (c.f., Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001).

Stimuli were presented one at a time at the center of the CRT in white lowercase letters against a black background. The experiment consisted of two blocks of 150 trials. The 300 experimental trials were preceded by 10 practice trials. Subjects were asked to pay attention to the first word and read the second word as quickly and accurately as possible. Each trial began with a fixation mark (+) appearing in the center of the screen for 2000 ms. The prime followed and appeared for 200 ms. The prime was replaced by the target, which remained on the screen until the initiation of the reading response. The experimenter then coded the trial as correct, incorrect, or noise (some extraneous noise triggered the voice key or it failed to be triggered by the reading response). A 2000 ms interval occurred between trials.

3.7. Structural magnetic resonance imaging

Structural magnetic resonance imaging (MRI) was performed on a Siemens 1.5 T Vision System (Erlangen, Germany). Between 2 and 4 high-resolution (1 mm × 1 mm × 1.25 mm) T1-weighted MP-RAGE scans were acquired per participant (TR = 9.7 ms, TE = 4 ms, flip angle = 10°, TI = 20 ms, TD = 200 ms). Scans were motion corrected and averaged, yielding a single image volume with high contrast-to-noise ratio, enabling quantitative characterization. All MRI scans were conducted within 6 months of neuropsychological testing and experiments.

3.8. Hemispheric brain volume

Single within-participant averaged volumes were interpolated to 1-mm isotropic voxels within the atlas space of Talairach and Tournoux (1988). *The atlas target consisted of merged young adult/older adult template that accommodates participant atrophy. Registration was verified for each individual*. An automated procedure then was used to segment each participant's image volume into cerebrospinal fluid (CSF), grey matter and white matter classes (computed separately for whole-brain and hemispheres) using the signal intensity histogram (Snyder, Sanders, Linenweber, Morris, & Buckner, 2000). Hemispheric brain volume percentages were then calculated for each participant as grey and white matter voxels divided by total within-hemisphere voxels (including CSF). Brain volume percentages were scaled to the volume of the atlas mask to compensate for individual head size. This normalization procedure is proportionate to normalization based on total intracranial volumes to compensate for differences in head size (Buckner et al., 2004).

3.9. Cortical thickness based on MRI

A sensitive cortical thickness analysis was employed to identify potentially small reductions in grey matter thickness in early dementia groups. Cortical thickness was derived using a series of procedures described in detail elsewhere (Dale et al., 1999; Fischl & Dale, 2000; Fischl et al., 1999a, b, 2001; Salat et al., 2004) and validated against both manual measurement from MRI patient populations (Kuperberg et al., 2003) and histology (Rosas et al., 2002). Briefly, white matter voxels within each participant's three-dimensional image volume were first classified using intensity and continuity information. The surface of the connected white-matter voxels was then deformed and inflated to locate the approximate pial surface and this information was refined to obtain a representation of grey-white matter boundary (Dale et al., 1999). Distance between representations of grey-white boundary and cortical surface was calculated at each point across the cortex to produce representations of cortical thickness (cortical thickness maps). Interpolation is used in this process to achieve subvoxel (below 1 mm) accuracy (Dale et al., 1999). Finally, thickness measures were mapped on the 'inflated' surface of each subject's reconstructed brain (Fischl et al., 1999a), allowing visualization of the entire cortical surface, including sulcal regions.

Mean group cortical thickness estimates were computed at each point on the reconstructed surfaces using a method that applies a series of steps to match morphologically homolo-

gous cortical locations across subjects (Fischl et al., 1999a). The method involved smoothing reconstructed surface maps using a symmetric Gaussian kernel with a standard deviation of 22 mm and then averaging across subjects using a non-rigid high-dimensional spherical method, which aligns cortical folding patterns (Fischl et al., 1999a). Group cortical thickness estimates were compared statistically using an implementation of the general linear model computed on the surface map data examining the effect of group on thickness at each vertex across the cortical mantle.

4. Results

Mean demographic information and scores representing estimated global dementia severity for SD, DAT and control groups are listed in Table 1. ANOVA revealed no significant age differences between the three groups ($F_{(2,27)} = 2.13$, $P = 0.14$). The SD group was significantly younger than the DAT group ($t_{(14)} = 2.49$, $P < 0.05$). DAT and control groups did not differ in age ($P = 0.46$). The three groups were matched for level of education. Patient groups were matched for general global severity of dementia as measured by both the CDR and the MMSE. Although neither measure provides an absolute index of dementia severity across different dementia subtypes, taken together they suggest similar levels of (mild) global dementia severity across groups.

Table 1
Mean demographic and general dementia severity data at the time of imaging

Variable	Control, $n = 14$	DAT, $n = 10$	SD, $n = 6$	ANOVA, P-value
Males/females	8/6	7/3	4/2	
Age	74.1 (9.0)	76.6 (5.7)	68.8 (6.5)	0.14*
Education	14.5 (2.6)	14.5 (3.2)	13.8 (2.0)	ns
MMSE	29 (1.1)	25 (4.7)	23 (1.7)	<0.001[a]
CDR	All 0	8 0.5/2 1	5 0.5/1 1	

Notes: Standard deviations are in parentheses.
* SD group significantly younger than DAT group ($P < 0.05$).
[a] SD and DAT groups both significantly worse than control group ($P < 0.01$) but not different from each other. ns: not significant.

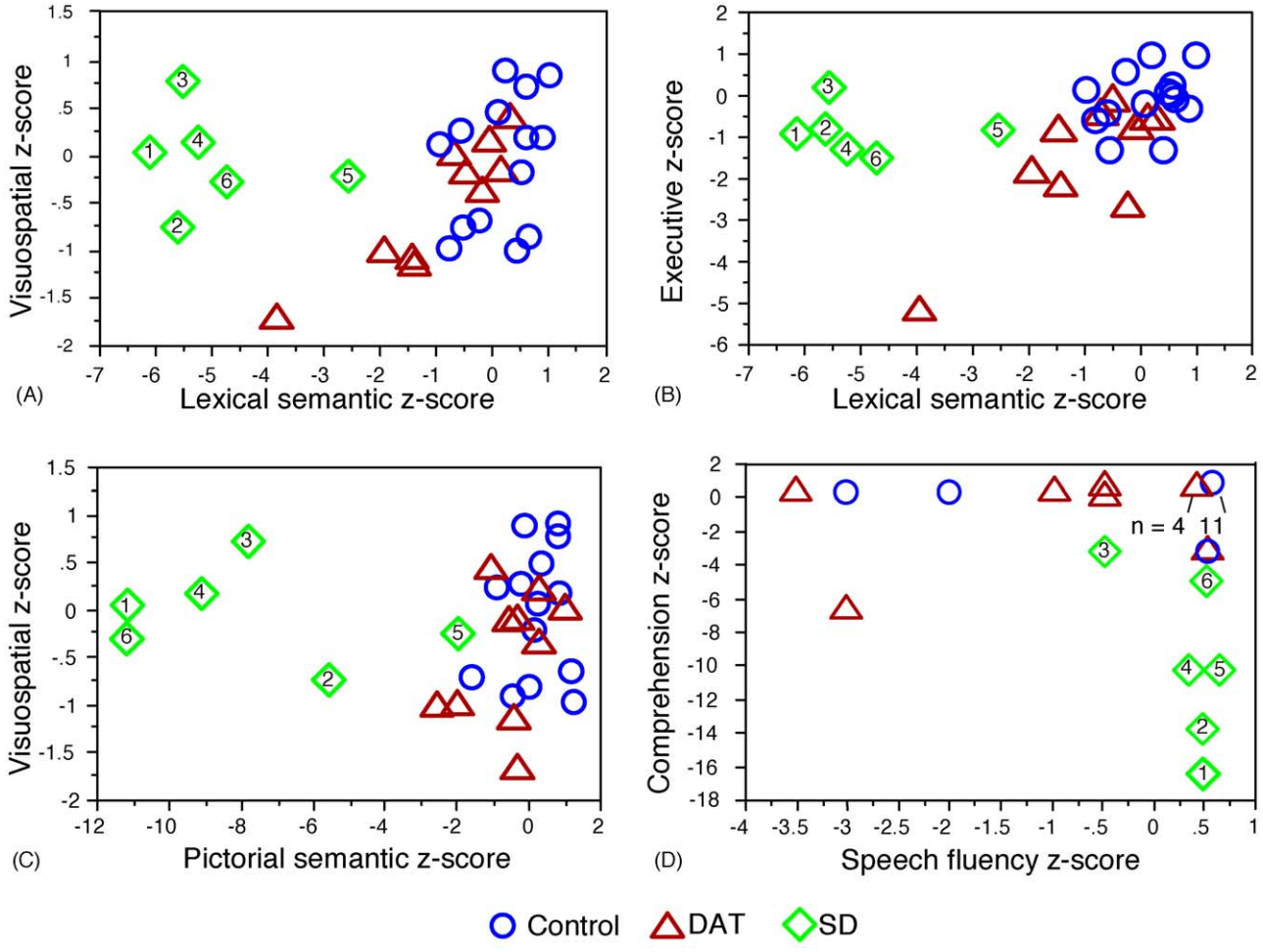

Fig. 1. Scatter plots of *z*-scores for all SD (green diamonds), DAT (red triangles) and control (blue circles) subjects across several composite cognitive domains (see methods section for list of tests within each domain). Numbers within green diamonds represent individual SD subjects (as in Table 2). *Z*-scores are scaled to the mean of the control group. Individual panels plot composite *z*-scores for domains of lexical semantic versus visuospatial (A); lexical semantic versus attentional-executive (B); pictorial semantic versus visuospatial (C); speech fluency versus comprehension (D).

4.1. Identifying semantic dementia

Raw scores from all tests used to identify SD individuals are presented in Table 2. Fig. 1 illustrates degrees of deviation (in standardized scores) of SD individuals from control and DAT subjects across several cognitive domains. The six SD individuals show patterns of impaired lexical semantics relative to visuospatial functioning (Panel A); impaired lexical semantic relative to attentional-executive functioning (Panel B); impaired pictorial semantics relative to visuospatial functioning (Panel C); impaired comprehension relative to speech fluency (Panel D). The overall profile in these individuals indicating breakdown of semantic knowledge across verbal and non-verbal domains with relative preservation of visuospatial and attentional-executive functioning and impaired comprehension relative to speech fluency meets the criteria established for SD (Hodges et al., 1992; Neary et al., 1998). As expected, several early DAT individuals show semantic impairment relative to controls. However, early DAT individuals tend to show less semantic impairment and more visuospatial and attentional-executive impairment than the early SD individuals.

4.2. Picture naming and picture recognition memory

Fig. 2 presents means and standard errors for the control, DAT and SD groups on the picture naming and picture recognition memory tests. As expected, there was an effect of group on naming performance ($F_{(2,26)} = 74.2$, $P < 0.0001$), with the SD group showing significantly poorer naming than the other groups (control: $t_{(17)} = 10.1$, $P < 0.0001$; DAT $t_{(13)} = 7.5$, $P < 0.0001$). The DAT group showed significantly poorer naming than the control group ($t_{(22)} = 2.5$, $P < 0.05$), however caution is needed in interpreting this result due to the relatively weaker (uncorrected) significance level.

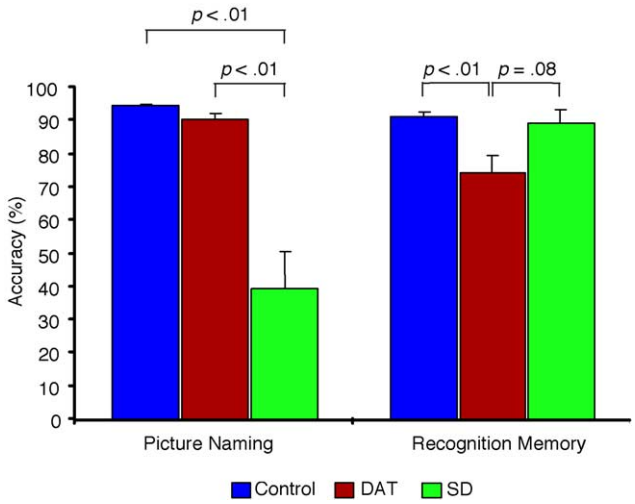

Fig. 2. Mean accuracy (in percent) for the control (blue), DAT (red) and SD (green) groups on the picture naming (left side) and picture recognition (right side) tests. Bars represent the standard error of the mean. Significant effects and trends are indicated at the top.

A significant effect of group was also found on the recognition memory task ($F_{(2,26)} = 7.6$, $P < 0.01$). In contrast to their very poor performance on the naming task, however, SD performance on the picture recognition memory task did not differ from that of the control group ($t_{(17)} = 0.6$, ns). By way of contrast, the DAT group showed significantly poorer picture recognition memory than the control group ($t_{(22)} = 3.6$, $P < 0.01$) and, despite the small sample size, there was a trend in the direction of poorer picture recognition memory in the DAT group than the SD group ($t_{(13)} = 1.9$, $P = 0.08$).

Effect sizes were calculated to assess the validity of the picture naming/recognition memory probe for early differentiation of SD and DAT by subtracting picture recognition memory scores from picture naming scores for individuals and across groups. The mean group effect sizes and standard deviations (in parentheses) were 3.0 (5.0), 16.2 (17.4), −49.7 (19.6) for the control, DAT and SD groups, respectively. Fig. 3 illustrates effect sizes of individual control, DAT and SD subjects. All SD subjects show large negative effect sizes (better recognition memory than naming), which separate them clearly from control and DAT subjects. Half of the DAT subjects show the reverse dissociation, with positive effect sizes (greater naming than recognition memory). However, half of the DAT individuals show little or no dissociation between recognition memory and naming, suggesting that the naming/recognition memory probe may be more sensitive to the identification of early SD than early DAT.

4.3. Word naming

Examination of response output revealed that all groups showed reading accuracies at ceiling (mean control group = 100%; mean DAT group = 99%; mean SD group =

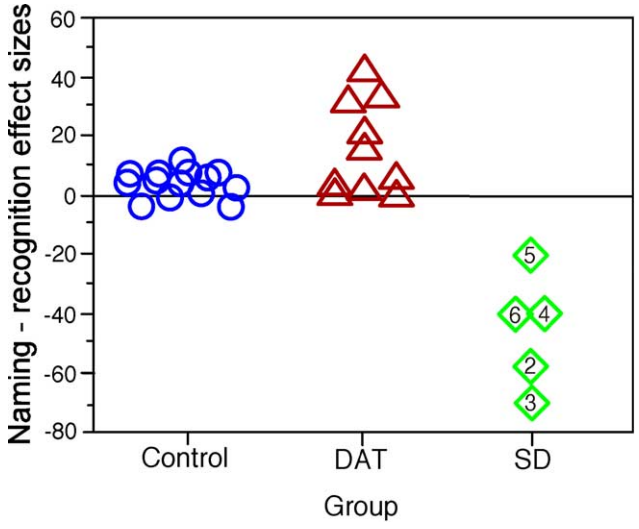

Fig. 3. Scatter plot of effect sizes for control (blue circles), DAT (red triangles), and SD (green diamonds), subjects for picture naming – picture recognition memory tests. Numbers within green diamonds represent individual SD subjects (as in Table 2, Fig. 1. SD 1 did not participate in this experiment).

Table 2
Mean group psychometric scores and individual SD scores

Test (maximum score)	Control, $n = 14$	DAT, $n = 10$	SD, $n = 6$	SD1	SD2	SD3	SD4	SD5	SD6
Boston naming (60)	55.4 (3.7)	48.4 (11.0)	14.8 (11.7)	5	6	8	16	36	18
Animal fluency	22.2 (4.3)	14.3 (4.6)	5.7 (2.0)	7	8	5	3	7	4
AMNART (45)	33.4 (6.8)	32.0 (4.1)	11.8 (8.8)	0	5	7	11	27	9
Category fluency	82.2 (15.4)	58.4 (20.5)	19.0 (7.1)	na	na	24	14	36	na
Synonym judgment (96)	89.8 (5.0)	86.8 (6.3)	66.0 (14.2)	na	55	61	na	82	na
Word-to-picture matching (64)	63.8 (0.4)	62.8 (1.5)	44.3 (17.5)	13	57	50	42	63	41
Picture sort (128)	125.6 (1.7)	124.2 (2.8)	116.6 (16.1)	116	110	118	118	121	na
Pyramids and palm trees									
Pictures (52)	50.9 (1.1)	49.8 (2.0)	38.8 (8.7)	26	48	36	35	49	39
Cookie theft picture (6)	5.8 (0.3)	5.9 (0.2)	5.9 (0.1)	6	6	5.8	6	6	6
Auditory comprehension (15)	14.9 (0.3)	14.8 (0.5)	12.3 (1.5)	10	11	14	12	12	14
Benton copy (10)	9.2 (1.8)	8.3 (3.5)	9.8 (0.4)	10	9	10	10	10	10
WAIS block design (48)	29.6 (9.0)	23.9 (13.0)	27.2 (10.4)	28	20	44	18	30	24
Raven's matrices (36)	30.3 (5.2)	23.6 (5.8)	30.2 (3.1)	32	31	34	29	25	30
VOSP									
Screening test (20)	19.5 (.0.8)	19.5 (0.7)	19.0 (1.8)	na	16	20	20	20	20
Dot counting (10)	9.6 (0.7)	9.9 (0.3)	10.0 (0.0)	na	10	10	10	10	10
Position discrimination (20)	19.1 (2.8)	19.9 (0.3)	20.0 (0.0)	na	20	20	20	20	20
Number location (10)	9.7 (0.6)	9.4 (0.7)	8.5 (0.9)	na	7	9	9	9	9
Cube analysis (10)	9.7 (0.6)	8.9 (1.0)	9.0 (1.0)	na	9	10	9	8	10
Digit span									
Forward	6.6 (1.2)	5.7 (1.1)	6.2 (0.8) 7	5	7	6	6	6	
Backward	5.1 (1.0)	3.8 (1.6)	4.3 (0.8) 4	4	6	4	4	4	
WAIS digit symbol (90)	47.9 (9.3)	31.8 (16.9)	39.8 (1.3)	41	39	41	39	38	41
Trails A (180)	36.2 (11.9)	61.9 (44.8)	47.8 (13.1)	58	38	37	65	34	55
Trails B (180)	106.2 (37.8)	144.8 (44.8)	122.0 (25.7)	144	115	85	114	158	116
Picture naming (64)	60.6 (1.6)	58.1 (3.3)	25.0 (13.6)	na	20	16	22	49	18
Picture recognition memory (32)	29.4 (1.6)	24.2 (5.7)	28.6 (2.9)	na	30	31	26	31	26

Notes: Standard deviations are in parentheses. AMNART: American Version of Nelson Adult Reading Test; Raven's Matrices: Raven's Colored Progressive Matrices; VOSP: Visual Object and Space Perception battery; na: not available.

98%). Therefore no formal analyses of accuracy data were undertaken.

4.4. Frequency and length effects

In order to explore possible frequency and length effects on naming latencies, words were sorted into 104 short (3, 4 letters, $M = 3.80$) and 59 long (5, 6 letters, $M = 5.26$) categories. Next, a median split was computed for the short words and was used to sort words into high ($M = 278.3$; $N = 52$) and low ($M = 28.6$; $N = 52$) frequency groups (Kucera & Francis, 1967). The median frequency value used to categorize short words was then applied to long words resulting in high ($M = 210.7$; $N = 27$) and low ($M = 20.9$; $N = 32$) frequency groups. Separate ANOVAs conducted on frequency and length values for the items used in the experiment indicated that high-frequency words were more frequent than low-frequency words, $F_{(1,159)} = 37.46$, $P < 0.01$, and longer words were longer than shorter words, $F_{(1,159)} = 395.80$, $P < 0.01$. No other tests were significant, all P's > 0.29, indicating that frequency and length were orthogonal factors.

Table 3 presents the mean group latencies for the naming experiment. The ANOVA involving the three groups revealed a main effect of group, $F_{(2,26)} = 3.54$, $P < 0.05$, a frequency effect, $F_{(1,26)} = 23.05$, $P < 0.01$, a length effect, $F_{(1,26)} = 13.72$, $P < 0.01$, a frequency by group interaction, $F_{(2,26)} = 4.41$, $P < 0.05$, a length by group interaction, $F_{(2,26)} = 5.98$, $P < 0.01$, and a frequency by length by group interaction, $F_{(2,26)} = 4.61$, $P < 0.05$. The frequency by length interaction was not significant, $P > 0.19$.

4.5. Healthy older adults versus individuals with DAT

The results from this analysis indicated that high-frequency words were responded to in less time than low-frequency words, $F_{(1,21)} = 7.57$, $P < 0.05$. Individuals with DAT were slower to respond than healthy older adults, but the effect of group only approached significance, $F_{(1,21)} = 3.18$, $P = 0.089$. No other effects were significant, all P's > 0.27.

Table 3
Mean group reading latencies split by frequency and length (standard deviations in parentheses)

Group	Low-frequency		High-frequency	
	Short	Long	Short	Long
Control ($n = 14$)	674 (99)	690 (113)	664 (96)	665 (107)
DAT ($n = 9$)	813 (251)	820 (258)	793 (249)	803 (263)
SD ($n = 6$)	888 (176)	941 (202)	800 (109)	894 (173)

4.6. Healthy older adults versus individuals with SD

The results from this analysis indicated that individuals with SD were slower to respond than healthy older adults, $F_{(1,18)} = 12.17$, $P < 0.01$. In addition, more frequent words were responded to in less time than less frequent words, $F_{(1,18)} = 19.79$, $P < 0.01$, and shorter words were responded to in less time than longer words, $F_{(1,18)} = 18.22$, $P < 0.01$. The frequency effect was significantly larger in SD than in controls, $F_{(1,18)} = 6.90$, $P < 0.05$, as was the length effect, $F_{(1,18)} = 11.60$, $P < 0.01$. There was a significant interaction among frequency, length, and group, $F_{(1,18)} = 12.46$, $P < 0.01$. A simple effects analysis indicated that the frequency by length by group interaction occurred because, in healthy older adults, the length effect was larger for low-frequency words, $t_{(13)} = 2.36$, $P < 0.05$ than high-frequency words, $t < 1$, but for individuals with SD, the length effect was similar for both low-frequency words, $t_{(5)} = 2.48$, $P = 0.056$, and high-frequency words, $t_{(4)} = 2.98$, $P < 0.05$.

4.7. Individuals with DAT versus individuals with SD

The results of this analysis indicated that more frequent words were responded to in less time than less frequent words, $F_{(1,13)} = 15.80$, $P < 0.01$, and shorter words were responded to in less time than longer words, $F_{(1,13)} = 8.83$, $P < 0.05$. Overall response times between the SD and DAT groups were not significantly different. Nevertheless, the SD group showed a larger frequency effect than the DAT group, $F_{(1,13)} = 4.97$, $P < 0.05$, and a larger length effect, $F_{(1,13)} = 5.61$, $P < 0.05$ than the DAT group. The SD group showed a frequency effect 3.5 times the size of the DAT (and control) group and a length effect over eight times the size the DAT (and control) group. It is important to note that the qualitatively different pattern obtained in SD cannot be attributable to processing speed *per se* because there was no main effect of group on response latencies, $F < 1$.

To confirm further that the disproportional effects of frequency and length on SD reading were not the result of generally slower reading, an analysis was conducted comparing the SD group with the six slowest readers in the DAT group. Table 4 presents mean latencies for the SD group and the DAT subgroup split by frequency and length effects. Overall response times between the SD and the DAT subgroup were not significantly different, $F < 1$. However, and despite the reduced power of this analysis, when compared to the slowest DAT readers, the SD group still showed a significantly larger frequency effect than the DAT group, $F_{(1,10)} = 5.49$, $P = 0.041$, and a marginally significantly longer length effect, $F_{(1,10)} = 4.22$, $P = 0.057$. There was no group by frequency by length interaction, $F < 1$.

Table 4
Mean reading latencies split by frequency and length for DAT subgroup matched on overall response latency with SD group (standard deviations in parentheses)

Group	Low-frequency		High-frequency		
	Short	Long	Short	Long	Mean RT
DAT ($n = 6$)	917 (244)	912 (268)	900 (233)	908 (257)	897
SD ($n = 6$)	888 (176)	941 (202)	800 (109)	894 (173)	881

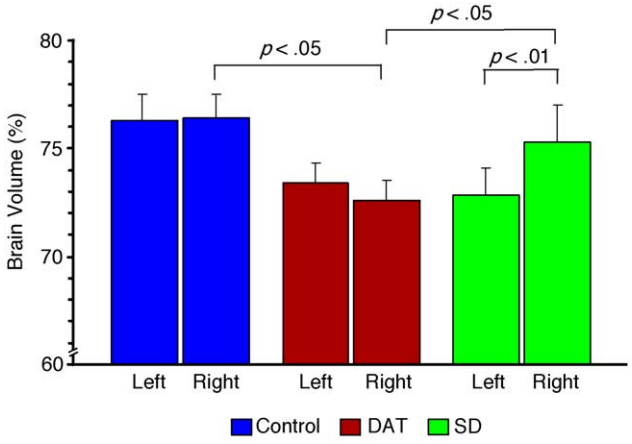

Fig. 4. Mean percentages of brain volume in left and right hemispheres of control (blue) DAT (red) and SD (green) groups. Bars represent the standard error of the mean.

4.8. Brain volume

Fig. 4 presents results from the automated atrophy assessment expressed as percentage of brain volume, as a function of group and hemisphere. Group differences in global atrophy were not significant (nor were differences in SD and DAT global atrophy, $P = 0.55$). There was a significant effect for more left hemisphere (LH) atrophy ($F_{(1,27)} = 8.9$, $P < 0.01$), an effect driven by the magnitude of the lateralized atrophy in the SD group. There was a significant group × hemisphere interaction in atrophy patterns ($F_{(2,27)} = 19.7$, $P < 0.0001$). Whereas the SD group showed significantly more atrophy in the LH ($t_{(5)} = 5.5$, $P < 0.01$), the DAT group showed a trend toward more atrophy in the RH ($t_{(9)} = 2.2$, $P = 0.06$). Fig. 4 shows that DAT and SD groups had similar degrees of LH atrophy, with the SD group distinguished by less RH atrophy.

4.9. Cortical thickness based on MRI

Fig. 5 presents surface maps of cortical thinning comparing SD and DAT groups. Cortical thinning in the SD group compared to the DAT group was found on the lateral surface of the left temporal lobe. Significant cortical thinning was observed in the left temporal pole. A much smaller region of thinning in the SD group was found in the right temporal pole. Focal temporal pole atrophy in SD is in keeping with results of several other studies which have shown atrophy focused primarily on anterior temporal lobe in SD, even at later dementia stages (Boxer et al., 2003; Mummery et al., 2000). Significant cortical thinning in the DAT group compared to the SD group was found in cinguloparietal cortex bi-

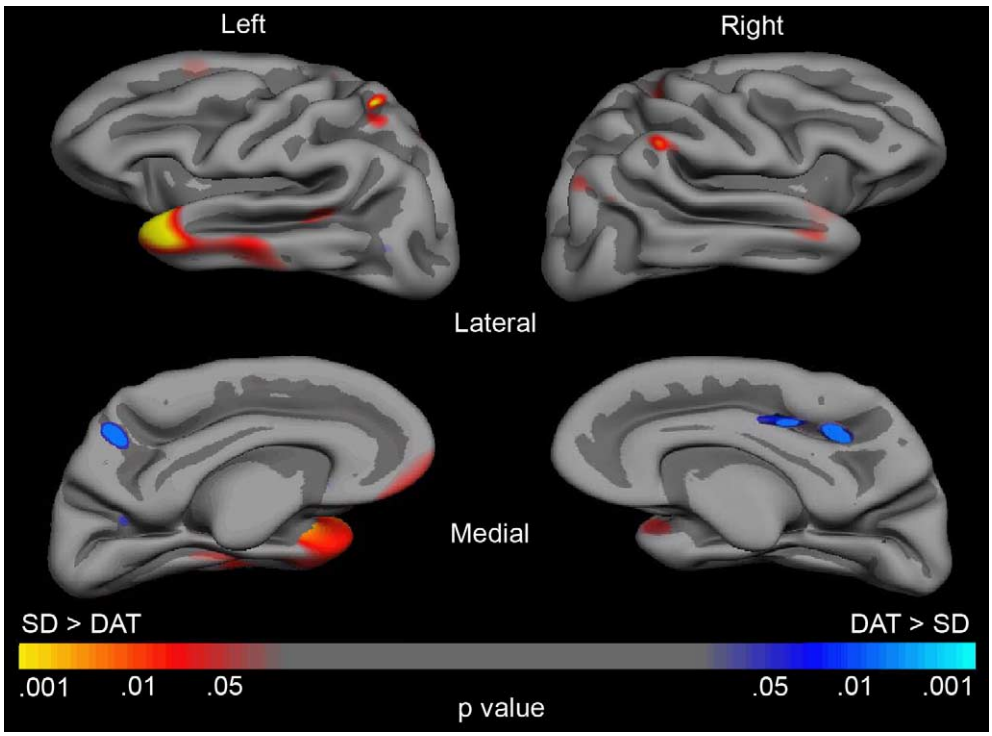

Fig. 5. Group maps of cortical thinning. Surface maps of cortical thinning were generated by assessing the influence of group on thickness (using an implementation of the general linear model) computed at each vertex across the cortical mantle. Maps are presented on the semi-inflated cortical surface of an average brain with dark grey regions representing sulci and light grey regions representing gyri. Non-neocortical regions and regions that are not part of the cortical mantle (such as the corpus collosum and thalamus) have been excluded from the analysis. The colorscale at the bottom represents the significance level of the group thickness difference. Regions with most significant thinning in the SD group compared to the DAT group are represented in yellow and regions with most significant thinning in the DAT group compared to the SD group are represented in bright blue.

laterally. However, DAT is well-established to involve early atrophy of medial temporal structures and such atrophy may have been missed due to the focus here on the cortex. For this reason, and because reading differences between DAT and control groups were small, we restrict interpretations of neuroanatomical-reading results to the SD group.

5. Discussion

Our results demonstrate that SD can be differentiated neuropsychologically from DAT at very mild-to-mild stages of dementia severity. In particular, the large effect sizes in the direction of better picture recognition memory than picture naming observed consistently across SD individuals demonstrates that tests of picture naming/recognition memory constitutes one simple, powerful probe for early differentiation of SD from DAT. The identification of an early SD group provided the opportunity to inform models of reading by exploring the influence of isolated lexical semantic impairment on reading regular words. Results demonstrated differential effects of frequency and length on SD, DAT and control group reading of regular words that have implications for models of reading. Finally, neuroanatomical results combined with disproportional effects of frequency and length on SD reading latencies suggest an important role for the left temporal pole in lexical/semantic components of reading and that damage to the region correlates with disruption of single word reading associated with increased reliance on sublexical processes. The discussion below elaborates on these findings.

5.1. Early SD and DAT can be differentiated neuropsychologically

Our results demonstrate that early SD and DAT (based upon standardize clinical measures and results indicating minimal whole-brain atrophy) are distinguishable neuropsychologically. Within SD and DAT groups, individuals at similar levels of mild dementia severity showed varying degrees of impairment in specific cognitive domains, particularly in degrees of semantic impairment. However, within-group variance was far outweighed by the distinct neuropsychological profiles observed between SD and DAT individuals. Early in the course of dementia, SD individuals show a striking multi-modal, multi-domain breakdown of semantic knowledge within the context of preserved visuospatial and attentional-executive functioning. In early DAT, semantic difficulty tended to be restricted to speeded tests with high executive demands (see Table 2) and was accompanied by deficits in visuospatial and/or general attentional-executive functioning.

5.2. A picture naming/recognition memory probe can differentiate early SD from DAT

The most powerful test for differentiation of early SD and DAT individuals was a picture naming/recognition memory probe. Recent research has observed a double dissociation between SD and DAT groups in picture naming and picture recognition memory, with SD groups showing poorer naming but better recognition memory than DAT groups (Graham et al., 1997, 2000a; Simons et al., 2002a). Suggestions of preserved episodic memory for pictures in the context of degraded semantic knowledge have been controversial (c.f., Tulving, 2001). Our results of a double dissociation in picture naming/recognition memory between SD and DAT groups replicate the preservation of episodic memory for pictures in SD despite degraded semantic knowledge (Graham et al., 1997, 2000a; Simons et al., 2002a, 2002b).

In addition to group differences observed, the important clinical implications regarding the potential for differential diagnosis raised by the Cambridge group's observations led us to explore the ability of a picture naming/recognition memory probe to differentiate early SD and DAT individuals. Our results demonstrate that a picture naming/picture recognition memory probe consistently differentiates SD individuals from both DAT and control (healthy older) individuals. As can be seen in Fig. 3, all SD individuals showed a large effect size of at least 20% points in the direction of better performance in recognition memory than naming, separating them clearly from DAT and control subjects. By contrast, while all DAT individuals showed superior naming compared to recognition memory, four showed naming scores within 5% points of their recognition memory scores, similar to control individuals. These results suggest that a picture naming/recognition memory probe is an important tool in early differentiation of SD from DAT but less sensitive to early differentiation of DAT from healthy older individuals.

5.3. Regular word reading is prolonged in early SD and DAT

The identification of an early SD group provided the opportunity to inform models of reading by exploring the influence of isolated lexical semantic impairment on reading regular words. Reading of regular words was highly accurate in both patient groups, consistent with previous results with SD (Patterson & Hodges, 1992) and DAT (Balota & Ferraro, 1993; Patterson et al., 1994a, 1994b). However, the present findings demonstrate that accurate translation of orthography-to-phonology of regular words requires a cost in processing speed in both early SD and DAT.

Turning to differential effects of lexical and sublexical variables on reading, we began by asking whether relatively graded effects might emerge between groups. Interestingly, although such effects did not emerge between SD and DAT groups in overall latency, only the SD group showed disproportional effects of frequency and length on reading: The SD group showed a frequency effect in reading 3.5 times that of DAT and control groups and a length effect over eight times that of DAT and control groups. The finding of increased response times in SD and DAT reading compared to those of a control group, combined with exaggerated effects of frequency and length only in SD, reveals clues about potentially different cognitive processes underlying reading in the three groups. These potentially different processes are first discussed with respect to dual-route and connectionist models and then in terms of SD group atrophy patterns.

The highly focal nature of the cognitive impairment in early SD suggests strongly that their increased naming latency relates to damaged lexical/semantic components of reading. In particular, all SD subjects showed impaired reading of words with irregular spelling-to-sound correspondences (see AMNART scores in Table 2). Impairment of irregular word reading has been interpreted as evidence damaged lexical (e.g., Blazely, Coltheart & Casey, in press) or semantic (e.g., Patterson & Hodges, 1992) components of reading. With respect to models of reading, the finding of a group by frequency interaction is readily accommodated within both dual-route and connectionist frameworks. Dual-route models (e.g., Coltheart, 1978; Coltheart et al., 2001) propose that words are read aloud via two processing routes. A lexical route maps orthographic strings directly onto lexical representations, where corresponding pronunciations are stored. In addition, a sublexical route translates print into sound serially via the application of grapheme-to-phoneme correspondence rules. The degradation of lexical representations in SD affects the efficiency of the lexical route. Within a dual-route account, disproportional frequency effects observed can be explained as a consequence of disproportionate loss of low-frequency words in the lexical route. A large body of data indicates that reading of low-frequency words are affected prior to high-frequency words in cases of lexical/semantic impairment (Gold & Kertesz, 2000; Schwartz, Saffran, & Marin, 1980; Warrington, 1975). Connectionist models (e.g., Plaut, McClelland, Seidenberg, & Patterson, 1996; Seidenberg & McClelland, 1989) can also explain the group by frequency interaction. Connectionist models propose that reading aloud is accomplished via a network of simple processing units that learns associations between inputs (i.e., orthography) and outputs (i.e., phonology). In addition, a semantic level interacts with orthographic and phonological levels. Here, a larger frequency effect in SD would result from damage to the semantic system. Due to graceful degradation (Bechtel & Abrahamsen, 1991), low-frequency words would be more disrupted in early-stage SD than high-frequency words. In other words, high-frequency words would receive a boost from semantics that would be less likely for low-frequency words, and this would produce an exaggerated frequency effect.

Unlike the group by frequency interaction, the group by length interaction is more easily accommodated within dual-route than connectionist models. According to the dual-route model, the large-scale damage incurred by the lexical route

in SD should lead to increased reliance on sublexical processes and resulting disproportional increases in latencies on longer words. Because the sublexical route is a serial processor, longer words should require more processing time than shorter words. For words with regular spelling-to-sound correspondences (such as those used here) the two routes arrive at the same pronunciation. Thus, the sublexical route would be expected to output accurate but slower pronunciation. This is exactly what happened. Interestingly, there is evidence of greater effects of length in reading pseudowords than words in normal readers (Weekes, 1997). This may be directly relevant to SD individuals, for whom the degree of lexical semantic impairment may render word reading somewhat analogous to pseudoword reading in normals. Unlike the SD group, the DAT group was not more influenced by length than control group. This would fit with the greater retention of lexical semantics in DAT compared to SD. In addition, mild attentional-executive impairment in early DAT is likely to contribute to their increased reading latencies relative to the control group (Balota & Faust, 2001; Balota & Ferraro, 1993, 1996; Paap & Noel, 1991). Connectionist models have a more difficult time accounting for the increased length effect observed in SD latencies because they do not contain a serial processing component. Rather, orthographic, phonological and semantic components of words are processed in parallel. Because the short and long words employed in the present study did not differ in terms of frequency, it is not clear how a connectionist model could predict that damage to semantics differentially would affect short and long words. It should be noted that simulations by Plaut et al. (1996, see p. 85) indicate that length actually does produce a reliable effect the model's settling times. However, this effect is relatively small (0.8%).

One specific connectionist theory, which can account for length effects in the context of semantic impairment is the "semantic glue" hypothesis (Patterson & Hodges, 1992). The theory holds that, in normal readers, the existence of a semantic representation corresponding to a pronunciation can serve to reinforce the correct response because an intact semantic representation reinforces the binding ("glue") thought to hold together phonological units for production. When insufficient residual word meaning is available, phonological elements of a response become "unglued" and pronunciation must be assembled from constituent elements, resulting in relatively longer reading latencies. The semantic glue theory is well suited to explain poor reading of irregular words in cases of semantic impairment because the strong weights on connections between orthography and phonology (stemming from the relative prevalence of regular spelling-to-sound correspondences) may operate without semantic constraint, leading to regularization errors. However, it is less clear how the theory could account for the present group by length interaction in latencies observed with regular words. Because the dual-route model makes relatively stronger predictions about the influence of length, and in particular the influence of length when the lexical route is disrupted, we believe it may be better able to accommodate the disproportional length effect observed in SD reading of regular words.

5.4. Neuroanatomical correlates of abnormal reading in SD and DAT

As expected from previous results comparing SD and DAT brain (Chan et al., 2001; Galton et al., 2001a, 2001b) and grey matter (Boxer et al., 2003; Mummery et al., 2000) volumes, significant cortical thinning in the SD group compared to the DAT (and control) group was observed in the left temporal pole. Unlike previous results, however, the present SD group showed atrophy restricted largely to left temporal pole, likely as a result of the mild dementia severity of the present sample. Direct contrast between the left and right hemisphere volumes in the SD group revealed a significant effect of lateralization. The relatively focal atrophy pattern in SD suggests that damage to anterior temporal cortex can be associated with disruption of regular word reading and allows us to consider the impact of damage to this region on reading. We note that it is also possible that other regions contribute to the behavioral pattern observed but were not identified in the present analyses. For discussion, we focus on the prominent difference in the left temporal pole.

The temporal pole has not typically been thought to play a significant role in normal reading. The modern neurological model of reading suggested three critical regions: left occipital cortex, involved in visual processing, left lateral parietotemporal cortex, involved in phonological and semantic coding, and a left inferior frontal cortex involved in the arranging of speech codes for output, and for output itself (Geshwind, 1965). Subsequent cognitive neuropsychological investigations suggested the involvement of additional regions in single word reading. For example, neuroanatomical localization in surface dyslexia has most frequently reported damage to posterior superior/middle temporal gyri and underlying white matter, suggesting the importance of posterior temporal lobe in lexical/semantic components of reading (Patterson, Marshall, & Coltheart, 1985). More recently, surface dyslexia has been reported in SD subjects showing atrophy focused primarily on the left temporal pole, and this has been interpreted as evidence that the region is importantly involved in semantic components of reading (Graham et al., 1994, 2000b; Hodges et al., 1992; Patterson & Hodges, 1992).

By contrast, less evidence exists that the temporal pole contributes to components of reading which do not stress semantics. First, SD patients with temporal pole atrophy and surface dyslexia have tended to show relatively accurate reading of words with regular spelling-to-sound correspondences (Graham et al., 2000b; Hodges et al., 1992; Patterson & Hodges, 1992), although impairment of regular word reading has been reported in some SD patients (Graham et al., 1994). Second, functional neuroimaging studies of single word reading (usually involving both regular and irregular words) have not tended to report prominent activation of temporal pole,

although activation of a number of anatomically proximal structures in left lateral temporal cortex have been reported including the superior, middle and inferior temporal gyri, depending upon the study (Fiez, Balota, Raichle, & Petersen, 1999; Howard et al., 1992; Petersen, Fox, Posner, Mintun, & Raichle, 1989; Price, Moore, Frackowiak, 1996; Pugh et al., 2000; Shaywitz et al., 2002).

The present findings of highly accurate reading in an SD group with focal thinning of temporal pole cortex in is in-line with a view that integrity of the left temporal pole does not appear strictly necessary for reading single regular words. However, the focal thinning of temporal cortex and disproportional influence of frequency and length on SD reading latencies for regular words suggests a role for the temporal pole in some component of regular word reading. Considered together, the present results suggest that the left temporal pole is importantly involved in lexical/semantic, but not orthographic or phonological, components of single word reading. The disproportional effects of frequency on SD latencies suggests that the left temporal pole represents a gateway to a lexical/semantic system that is particularly important for establishing the pronunciation of low-frequency regular (in addition to irregular) words. Such a system may typically serve to stabilize pronunciation of low-frequency words, which have weaker phonologically based lexical representations than high-frequency words, due to less experience with their orthographic-to-phonological transformations. Damage to a brain region associated with lexical/semantic components of reading would be expected to result in disproportional effects of length on reading latencies because it would increase reliance on serial, sublexical components of reading, and this is what resulted in the SD group. In general agreement with a role for left temporal pole in lexical/semantic components of reading, several functional neuroimaging studies have reported prominent activation of the region during word retrieval cued by a variety of stimuli (Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Grabowski et al., 2003) as well as during more explicit semantic analysis (e.g., Vandenberghe, Nobre, & Price, 2002; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996).

The pattern of reading and atrophy results from our SD group suggests further that left temporal pole is unlikely to be involved in orthographic processes associated with letter analysis, or in phonological processes associated with deriving sound from visual words sublexically. Disturbance in orthographic processing can actually produce exaggerated effects of length in single word reading as seen our SD group. In fact, disproportional length effects in reading have most commonly been reported in pure alexia (Dejerine, 1892), a reading disorder associated with impairment of processing letters groups (Patterson & Kay, 1982) or the analysis of individual letters (Arguin & Bub, 1993). However, the nature of the orthographic disturbance in pure alexia is associated with a stereotyped letter-by-letter reading strategy resulting in response times typically several seconds longer than normal readers (Bub, Black, & Howell, 1989; Patterson & Kay, 1982). In terms of phonological reading processes, the complete absence of reading errors in our early SD group, in the context of the severe lexical semantic impairment, suggests that the left temporal pole is not critically involved in deriving sound from visual words sublexically. Taken together, the present data suggest a role for the left temporal pole in lexical/semantic components of reading and demonstrate that cortical differences in this region associate with reliance on sublexical components of reading.

6. Conclusions

In conclusion, SD can be differentiated from DAT at mild dementia stages. While clinical overlap exists, the characteristic profile of relatively isolated multi-modal, multi-domain breakdown of semantic knowledge appears early in the course of SD, distinguishing it from DAT. The pattern of SD and DAT scores on picture naming and picture recognition memory tests suggest that these measures represent a simple, powerful probe for early differentiation of SD from DAT. In terms of reading, the relative influence of lexical and sublexical variables on group latencies is accommodated by dual-route models of reading and raises a challenge for most connectionist models. Finally, results of disproportional influence of frequency and length on SD reading combined with cortical thinning in the left temporal pole suggest a role for the region in lexical/semantic components of reading and demonstrate that differences in the left temporal pole associate with reliance on sublexical components of reading.

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References

Arguin, M., & Bub, D. N. (1993). Single-character processing in a case of pure alexia. *Neuropsychologia*, *31*, 435–458.

Armitage, S. G. (1945). An analysis of certain psychological tests used for the evaluation of brain injury. *Psychological Monographs*, *60*, 1–48.

Balota, D. A., & Faust, M. E. (2001). Attention in Alzheimers disease. In F. Boller & S. Cappa (Eds.), *Handbook of Neuropsychology: 6* (2nd ed., pp. 51–80). Elsevier.

Balota, D. A., & Ferraro, F. R. (1993). A dissociation of frequency and regularity effects in pronunciation performance across young adults, older adults, and individuals with senile dementia of the Alzheimer type. *Journal of Memory and Language*, *32*, 573–592.

Balota, D. A., & Ferraro, F. R. (1996). Lexical, sublexical and implicit memory processes in healthy young and healthy older adults and in individuals with dementia of the Alzheimer type. *Neuropsychology*, *10*, 82–95.

Bechtel, W., & Abrahamsen, A. (1991). *Connectionism and the mind: An introduction to parallel processing in networks*. Cambridge, MA: Blackwell.

Berg, L., McKeel, D. W., Jr., Miller, J. P., Storandt, M., Rubin, E. H., Morris, J. C., et al. (1998). Clinicopathologic studies in cognitively healthy aging and Alzheimer's disease: Relation of histologic markers to dementia severity, age, sex and apolipoprotein E genotype. *Archives of Neurology*, *55*, 326–335.

Blazely, A. M., Coltheart, M., & Casey, B. J. (in press). Semantic impairment with and without surface dyslexia: Implications for models of reading. *Cognitive Neuropsychology*.

Boxer, A. L., Rankin, K. P., Miller, B. L., Schuff, N., Weiner, M., Gorno-Tempini, M., et al. (2003). Cinguloparietal atrophy distinguishes Alzheimer disease from SD. *Archives of Neurology*, *60*, 949–956.

Bozeat, S., Lambon Ralph, A., Patterson, K., Garrard, P., & Hodges, J. R. (2000). Non-verbal semantic impairment in SD. *Neuropsychologia*, *38*, 1207–1215.

Bub, D., Black, S. E., & Howell, J. (1989). Word recognition and orthographic context. *Brain and Language*, *37*, 357–376.

Buckner, R. L., Head, D., Parker, J., Fotenos, A. F., Marcus, D., Morris, J. C., et al. (2004). A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. *NeuroImage*, *23*, 724–738.

Chan, D., Fox, N. C., Scahill, R. I., Crum, W. R., Whitwell, J. L., Leschziner, G., et al. (2001). Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's Disease. *Annals of Neurology*, *49*, 433–442.

Chertkow, H., & Bub, D. (1990). Semantic memory loss in dementia of Alzheimer's type. *Brain*, *113*, 397–417.

Coltheart, M. (1978). Lexical access in simple reading tasks. In G. Underwood (Ed.), *Strategies of Information Processing* (pp. 151–216). San Diego, CA: Academic Press.

Coltheart, M., Rastle, K., Perry, C., Langdon, R., & Ziegler, J. (2001). DRC: a dual route cascaded model of visual word recognition and reading aloud. *Psychological Review*, *108*, 204–256.

Cortese, M. J., Balota, D. A., Sergent-Marshall, S. D., & Buckner, R. L. (2003). Spelling via semantics and phonology: Exploring the effects of age. Alzheimer's disease and primary semantic impairment. *Neuropsychologia*, *41*, 952–967.

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *NeuroImage*, *9*, 179–194.

Damasio, H., Grabowski, T. J., Tranel, D., Hichwa, R. D., & Damasio, A. R. (1996). A neural basis for lexical retrieval. *Nature*, *380*, 499–505.

Dejerine, J. (1892). Contributions a l'etude anatomopathologique et clinique des differentes varietes de cecite verbale. *Memories de la Societé Biologique*, *44*, 61–90.

Fiez, J. A., Balota, D. A., Raichle, M. E., & Petersen, S. E. (1999). Effects of lexicality, frequency, and spelling-to-sound consistency on the functional anatomy of reading. *Neuron*, *24*, 205–218.

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences USA*, *97*, 11050–11055.

Fischl, B., Liu, A., & Dale, A. M. (2001). Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. *Institute of Electrical Electronics Engineers: Transactions in Medical Imaging*, *20*, 70–80.

Fischl, B., Sereno, M. I., & Dale, A. M. (1999). Cortical surface-based analysis II: inflation, flattening, and a surface-based coordinate system. *NeuroImage*, *9*, 195–207.

Fischl, B., Sereno, M. I., Tootell, R. B. H., & Dale, A. M. (1999). High-resolution inter-subject averaging and a coordinate system for the cortical surface. *Human Brain Mapping*, *8*, 272–284.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-Mental State: a practical method for grading the cognitive state of patients for the clinicians. *Journal of Psychiatric Research*, *12*, 189–198.

Galton, C. J., Gomez-Anson, B., Antoun, N., Scheltens, P., Patterson, K., Graves, M., et al. (2001). Temporal lobe rating scale: application to Alzheimer's disease and frontotemporal dementia. *Journal of Neurology, Neurosurgery and Psychiatry*, *70*, 165–173.

Galton, C. J., Patterson, K., Graham, K., Lambon-Ralph, M. A., Williams, G., Antoun, N., et al. (2001). Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology*, *57*, 216–225.

Geshwind, N. (1965). Disconnexion syndromes in animals and man. *Brain*, *88*, 17–294.

Gold, B. T., & Kertesz, A. (2000). Preserved visual lexicosemantics in global aphasia: A right-hemisphere contribution? *Brain and Language*, *75*, 359–375.

Goodglass, H., & Kaplan, E. (1983). *The Assessment of Aphasia and Related Disorders* (2nd ed.). Philadelphia: Lea and Febiger.

Grabowski, T. J., Damasio, H., Tranel, D., Cooper, G. E., Boles Ponto, L. L., & Watkins, G. L. (2003). Residual naming after damage to the left temporal pole: a PET activation study. *NeuroImage*, *19*, 846–860.

Graham, K. S., Becker, J. T., & Hodges, J. R. (1997). On the relationship between knowledge and memory for pictures: Evidence from the study of patients with semantic dementia and Alzheimer's disease. *Journal of the International Neuropsychological Society*, *3*, 534–544.

Graham, K. S., Hodges, J. R., & Patterson, K. (1994). The relationship between comprehension and oral reading in progressive fluent aphasia. *Neuropsychologia*, *32*, 299–316.

Graham, N. L., Patterson, K., & Hodges, J. R. (2000). The impact of semantic memory impairment on spelling: Evidence from semantic memory. *Neuropsychologia*, *32*, 299–316.

Graham, K. S., Simons, J. S., Pratt, K. H., Patterson, K., & Hodges, J. R. (2000). Insights from SD on the relationship between episodic and semantic memory. *Neuropsycholgia*, *38*, 313–324.

Grober, E., & Sliwinski, M. (1991). Development and validation of a model for estimating premorbid verbal intelligence in the elderly. *Journal of Clinical and Experimental Neuropsychology*, *13*, 933–949.

Hodges, J. R., & Patterson, K. (1995). Is semantic memory consistently impaired early in the course of Alzheimer's disease? Neuroanatomical and diagnostic implications. *Neuropsychologia*, *33*, 441–459.

Hodges, J. R., Garrard, P., & Patterson, K. (1998). Semantic dementia. In A. Kertesz & D. G. Munoz (Eds.), *Pick's Disease and Pick Complex* (pp. 83–104). New York: Wiley-Liss.

Hodges, J. R., Patterson, K., Oxbury, S., & Funnell, E. (1992). Semantic dementia: Progressive fluent aphasia with temporal lobe atrophy. *Brain*, *115*, 1783–1806.

Hodges, J. R., Patterson, K., Ward, R., Garrard, P., Bak, T., Perry, R., et al. (1999). The differentiation of semantic dementia and frontal lobe dementia (temporal and frontal variants of frontotemporal dementia) from early Alzheimer's disease: A comparative neuropsychological study. *Neuropsychology*, *13*, 31–40.

Howard, D., & Patterson, K. (1992).*Pyramids and Palm Trees: A Test of Semantic Access from Pictures and Words*. Thames Valey Publishing.

Howard, D., Patterson, K., Wise, R., Brown, W. D., Friston, K., Weiller, C., et al. (1992). The cortical localization of the lexicons: Positron emission tomography evidence. *Brain*, *115*, 1769–1782.

Huff, F. J., Corkin, S., & Growden, J. H. (1986). Semantic impairment and anomia in Alzheimer's disease. *Brain and Language*, *28*, 235–249.

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *Boston Naming Test*. Philadelphia: Lea and Febiger.

Kertesz, A., Appell, J., & Fisman, M. (1986). The dissolution of language in Alzheimer's disease. *Canadian Journal of Neurological Sciences*, *13*, 415–418.

Kertesz, A., Hudson, L., Mackenzie, I. R., & Munoz, D. G. (1994). The pathology and nosology of primary progressive aphasia. *Neurology*, *44*, 2065–2072.

Kucera, H., & Francis, W. N. (1967). *The computational analysis of present-day American English*. Brown University Press.

Kuperberg, G. R., Broome, M., McGuire, P. K., David, A. S., Eddy, M., Ozawa, F., et al. (2003). Regionally localized thinning of the cerebral cortex in schizophrenia. *Archives of General Psychiatry*, *60*, 878–888.

Martin, A., & Fedio, P. (1983). Word production and comprehension in Alzheimer's disease: The breakdown of semantic knowledge. *Brain and Language*, *19*, 124–141.

Mesulam, M. M. (1982). Slowly progressive aphasia without generalized dementia. *Annals of Neurology*, *11*, 592–598.

Mesulam, M. M. (2001). Primary progressive aphasia. *Annals of Neurology*, *49*, 425–432.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology*, *34*, 934–939.

Morris, J. C. (1993). The clinical dementia rating (CDR): current version and scoring rules. *Neurology*, *43*, 2412–2414.

Mummery, C. J., Patterson, K., Price, C. J., Ashburner, J., Frackowiak, R. S. J., & Hodges, J. R. (2000). A voxel-based morphometry study of semantic dementia: Relationship between temporal lobe atrophy and semantic memory. *Annals of Neurology*, *47*, 36–45.

Neary, D., Snowden, J. S., Gustafson, L., Passant, U., Stuss, D., Black, S., et al. (1998). Frontotemporal lobar degeneration: A consensus on clinical diagnostic criteria. *Neurology*, *51*, 1546–1554.

Paap, K. R., & Noel, R. W. (1991). Dual route models of print to sound: Still a good horse race. *Psychological Research*, *53*, 13–24.

Patterson, K., & Hodges, J. R. (1992). Deterioration of word meaning: Implications for reading. *Neuropsychologia*, *30*, 1025–1040.

Patterson, K., & Kay, J. (1982). Letter-by-letter reading: Psychological descriptions of a neurological syndrome. *Quarterly Journal of Experimental Psychology*, *34*, 411–441.

Patterson, K., Graham, N., & Hodges, J. R. (1994a). Reading in dementia of the Alzheimer type: A preserved ability? *Neuropsychology*, *8*, 395–407.

Patterson, K., Graham, N., & Hodges, J. R. (1994b). The impact of semantic memory loss on phonological representations. *Journal of Cognitive Neuroscience*, *6*, 57–69.

Patterson, K. E., Marshall, J. C., & Coltheart, M. (1985). *Surface dyslexia: Neuropsychological and cognitive studies of phonological reading*. London: Erlbaum Associates.

Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M., & Raichle, M. E. (1989). Positron emission tomographic studies of the processing of single words. *Journal of Cognitive Neuroscience*, *1*, 153–170.

Plaut, D. C., McClelland, J. D., Seidenberg, M. S., & Patterson, K. (1996). Understanding normal and impaired word reading: Computational principles in quasi-regular domains. *Psychological Review*, *103*, 56–115.

Price, C. J., Moore, C. J., & Frackowiak, R. S. (1996). The effect of varying stimulus rate and duration on brain activity during reading. *NeuroImage*, *3*, 40–52.

Pugh, K. R., Mencl, W. E., Shaywitz, B. A., Shaywitz, S. E., Fulbright, R. K., Constable, R. T., et al. (2000). The angular gyrus in developmental dyslexia: Task-specific differences in functional connectivity within posterior cortex. *Psychological Science*, *11*, 51–56.

Raven, J. C. (1995). *Colored Progressive Matrices Sets A, Ab, B*. Oxford Psychological Press Ltd.: Oxford.

Rosas, H. D., Liu, A. K., Hersch, S., Glessner, M., Ferrante, R. J., Salat, D. H., et al. (2002). Regional and progressive thinning of the cortical ribbon in Huntingtons disease. *Neurology*, *58*, 695–701.

Salat, D. H., Buckner, R. L., Snyder, A. Z., Greve, D. N., Desikan, R. S., Busa, E., et al. (2004). Thinning of the cerebral cortex in aging. *Cerebral Cortex*, *14*, 721–730.

Schwartz, M. F., Saffran, E. M., & Marin, O. S. M. (1980). Fractionating the reading process in dementia: Evidence for word-specific print-to-sound associations. In M. Coltheart, K. Patterson, & J. C. Marshall (Eds.), *Deep Dyslexia* (pp. 259–269). Routledge: London.

Seidenberg, M. S., & McClelland, J. L. (1989). A distributed, developmental model of word recognition and naming. *Psychological Review*, *96*, 523–568.

Shaywitz, B. A., Shaywitz, S. E., Pugh, K. R., Mencl, W. E., Fulbright, R. K., Skudlarski, P., et al. (2002). Disruption of posterior brain systems for reading in children with developmental dyslexia. *Biological Psychiatry*, *52*, 101–110.

Simons, J. S., Graham, K. S., & Hodges, J. R. (2002). Perceptual and semantic contributions to episodic memory: evidence from semantic dementia and Alzheimer's disease. *Journal of Memory and Language*, *47*, 197–213.

Simons, J. S., Verfaellie, M., Galton, C. J., Miller, B. L., Hodges, J. R., & Graham, K. S. (2002). Recollection-based memory in frontotemporal dementia: implications for theories of long-term memory. *Brain*, *125*, 2523–2536.

Snodgrass, J. G., & Vanderwart, M. A. (1980). standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. *Journal of Experimental Psychology: Human Learning and Memory*, *6*, 174–215.

Snowden, J. S., Goulding, P. J., & Neary, D. (1989). Semantic dementia: A form of circumscribed cerebral atrophy. *Behavioral Neurology*, *2*, 167–182.

Snyder, A. Z., Sanders, A. L., Linenweber, W., Morris, J. C., & Buckner, R. L. (2000). Automated atrophy assessment AAA in young middle-age nondemented and demented older adults. *Journal of Cognitive Neuroscience Supplement*, *2*, 115E.

Talairach, J., & Tournoux, P. (1988). *Co-planar Stereotaxic Atlas of the Human Brain*. New York: Thieme.

Tulving, E. (2001). Episodic memory and common sense: how far apart? *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, *356*, 1505–1515.

Vandenberghe, R., Nobre, A. C., & Price, C. J. (2002). The response of the left temporal cortex to sentences. *Journal of Cognitive Neuroscience*, *15*, 550–560.

Vandenberghe, R., Price, C., Wise, R., Josephs, O., & Frackowiak, R. S. (1996). Functional anatomy of a common semantic system for words and pictures. *Nature*, *383*, 254–256.

Warrington, E. K. (1975). The selective impairment of semantic memory. *Quarterly Journal of Experimental Psychology*, *27*, 635–657.

Warrington, E. K., & James, M. (1991). *The Visual Object and Space Perception Battery*. Bury St. Edmunds, UK: Thames Valley Test Company.

Wechsler, D. (1955). *Wechsler Adult Intelligence Scale*. New York: Psychological Corporation.

Wechsler, D., & Stone, C. P. (1973). *Wechsler Memory Scale*. Psychological Corporation: New York.

Weekes, B. S. (1997). Differential effects of number of letters on word and nonword naming latency. *Quarterly Journal of Experimental Psychology: Human Experimental Psychology*, *50*, 439–456.